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RESEARCH ARTICLE

Treatment Management in Acute Exacerbation of COPD in the Emergency Department: Dilemma in Oxygen Therapy

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HIGHLIGHTS

- In this study, it was aimed to compare the treatment efficacy of jet nebulizer and oxygen supply connected to a central system in the treatment of acute exacerbation of COPD.
- It was found that patients' blood gas parameters significantly improved in treatments applied with nebulizers.
- In this study, it was found that the blood gas parameters of patients treated with nebulizer improved better than the other group. Therefore, we recommend the use of nebulizers in the treatment of acute exacerbation of COPD in the emergency department.

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ABSTRACT

In this study, we aimed to compare the effectiveness of jet nebulizer and oxygen supply connected to the central system with a mask in the treatment of acute exacerbation of chronic obstructive pulmonary disease (COPD). A randomized, prospective, single-center clinical trial was conducted on patients admitted to the emergency department for acute exacerbation of COPD, diagnosed with guidelines provided by Global Initiative for Chronic Obstructive Lung Disease. The patients were randomized into two groups; the first group was applied treatment with jet-nebulizer, and the second group treatment applied with oxygen supply connected to the central system. Vital signs and arterial blood gas parameters were investigated. The mean age of the included 167 patients was 69.9±10 and 66% of them were male. In terms of the effectiveness of the treatments, the respiratory rate, among the vital signs, and pCO2, among the blood gas parameters were statistically decreased in the nebulizer group. Moreover, pO2 and sO2 levels were statistically increased in the nebulizer treatment group compared to the other group. It was found that patients' blood gas parameters significantly improved in treatments applied with nebulizers. Nebulizers should be preferred in the emergency department for the treatment of acute exacerbation of COPD.

Contents

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a respiratory tract disease characterized by a progressive, chronic and inflammatory response. Although it is one of the leading causes of mortality and morbidity in the world, it is a preventable and treatable disease [1, 2]. COPD is characterized by acute exacerbations, often patients present to the emergency room. These acute exacerbations significantly increase mortality and morbidity in COPD [3]. It was found that 46% of patients with COPD had an acute exacerbation at least once a year, and 19% of them were hospitalized [4].

Acute exacerbation of COPD is characterized by shortness of breath, cough, increased sputum and purulence, which leads to the changes in the patient's daily respiratory function and medication needs [4–6]. In addition, the increased frequency of acute exacerbation of COPD is an indicator of disease severity and is an indicator of poor prognosis [7].

Inhaled bronchodilators, systemic corticosteroids, systemic antibiotherapy and oxygen are used in the treatment of acute exacerbation of COPD [2, 5, 6, 8]. Various devices are used to administer these inhaler agents [4, 5, 9]. In emergency departments, inhaler therapy is usually given with a supply connected to the central system through simple or venturi face masks. In addition, nebulizer, non-invasive or invasive mechanical ventilators can be used in inhaler therapy. Nebulizers, one of these devices, turn the liquid drug into aerosol and deliver it directly to the airways and lungs in a short time [10]. Nebulizers, which are frequently used in emergency services, increase drug efficacy and prevent hypercapnia in patients. However, inhaler drugs can be administered to the patients in emergency services and during the transportation of patients to the hospital, by using central system pressure with a mask instead of a nebulizer. [10]. It should be kept in mind that oxygen therapy provided by the central system may cause hypercapnia in the treatment of acute exacerbation of COPD. In this study, it was aimed to compare the oxygen supply connected to the central system and jet nebulizer application in the treatment of acute exacerbation of COPD.

2. Methods

2.1. Ethical Statement

All patients participating in the study were informed and their consents were obtained. This study complied with the principles of Good Clinical Practice of the Declaration of Helsinki. In this study, approved by the research ethics review committee of the Atatürk University Clinical Research Ethics Committee (dated October 04, 2019, numbered 06/46).

2.2. Study Design

This is a randomized, prospective, single-center clinical trial, conducted in patients who admitted to the emergency department for acute exacerbation of COPD. But, the study could not be done in the double-blind method, because a nebulizer device was used in our study. The study was carried out in the emergency department of a tertiary university hospital that provides healthcare to 12 surrounding cities and nearly 4.5 million people.

2.3. Patients

Patients who came to the emergency department with complaints of shortness of breath were included in the study. Among these patients, patients who were diagnosed with COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [1] and presented with acute exacerbation were assigned to the groups consecutively. Patients older than 18 years who gave consent to participate in the study were included in the study. Those who are under the age of 18, who are unstable, who do not give their consent and/or cannot give their consent, who cannot tolerate treatment with a mask, who have shortness of breath due to reasons other than COPD, pregnant women, who are allergic to any of the drugs in the treatment protocol, who have cognitive or psychiatric disorders, need non-invasive or invasive mechanical ventilation patients were excluded from the study.

2.4. Groups

Group 1: Treatment group with jet nebulizer: COPD exacerbation treatment applied with jet nebulizer (Reichberg® RB 139 inhaler Aerosol Nebulizzatore, Germany).

Group 2: Treatment group with oxygen supply connected to central system: COPD exacerbation treatment will be given through the hospital central oxygen system. According to the GOLD guideline, COPD exacerbation therapy will be given at 6 L / min with a mask through the oxygen source connected to the central system. During the treatment, 2 L / min oxygen was given to the patients through the nasal cannula with the oxygen supply connected to the central system.

2.5. Treatment Protocol

Exacerbation treatment was administered to patients diagnosed with the GOLD guidelines. The patients were divided into two groups by computer-assisted randomization method. The randomization table was created via the website

randomizer.org. Salbutamol 2.5 mg, a short-acting β-2 agonist (Ventolin nebules®, GlaxoSmithKline Australia Pty. Ltd., Australia) and a short-acting anticholinergic ipratropium bromide 250 µg/2 ml (Atrovent®, Boehringer Ingelheim Drug Company, France) delivered as an inhaler with a reservoir nebul mask. This treatment was repeated 3 times in total, in every 20 minutes. Methylprednisolone, a systemic corticosteroid 1 mg/kg (Prednol-L® 40 mg ampoule, Mustafa Nevzat İlaç Sanayii A.Ş. Turkey), Teofilin 5 mg/kg (Aminocardol® ampoule 0.24 g/10 cc, Novartis, Turkey), and Ceftriaxone 1 g (Desefin® vial 1 g, Deva Holding A.Ş. Turkey) were administered intravenously. In addition, during the treatment period, 2 L / min oxygen therapy was applied to all patients with a nasal cannula and an oxygen source connected to the central system.

2.6. Arterial Blood Gas Uptake

Blood samples were taken from the radial artery for arterial blood gas measurement from the patients. First of all, the procedure was explained to the patient and the radial artery was palpated. After the area to be treated was determined, it was cleaned with 10% povidone iodine. With a heparinized blood gas injector, 2-3 ml of blood sample was taken by entering at an angle of 60° towards the pulsation direction. This procedure was repeated twice, before and after the treatment of acute exacerbation of COPD.

2.7. Measurements

Sociodemographic characteristics of the patients, such as age, gender, smoking, smoking amount in packs/years, smoke exposure, presence of condenser and chronic disease were recorded. Vital findings (systolic blood pressure, diastolic blood pressure, heart rate, oxygen saturation level and fever) and blood gas parameters (pH, pCO_2, pO_2, sO_2, HCO_3, lactate, base gap) during the admission to the emergency service and after COPD acute exacerbation treatment) were measured. In addition, the white blood cell count and serum creatinine values of the patients were also measured at the time of admission.

2.8. Analysis

SPSS version 25.0 (Armonk, NY, IBM Corp.) program was used for statistical analysis. The Shapiro – Wilk test was used for the estimation of normal distribution. Descriptive statistics are given as frequency (n) and percentage (%) for categorical variables, mean and standard deviation was given if data is normally distributed, and as median and interquartile range (IQR) for variables that do not show normal distribution. Comparison of groups for variables with normal distribution was made by Student's t-test, and for variables without normal distribution, group comparisons were made by Mann-Whitney U test. Chi-square test was used to compare groups in categorical variables. Wilcoxon test was used to compare the treatment efficacy of the groups before and after treatment. A Statistical significance level of $p < 0.05$ was accepted.

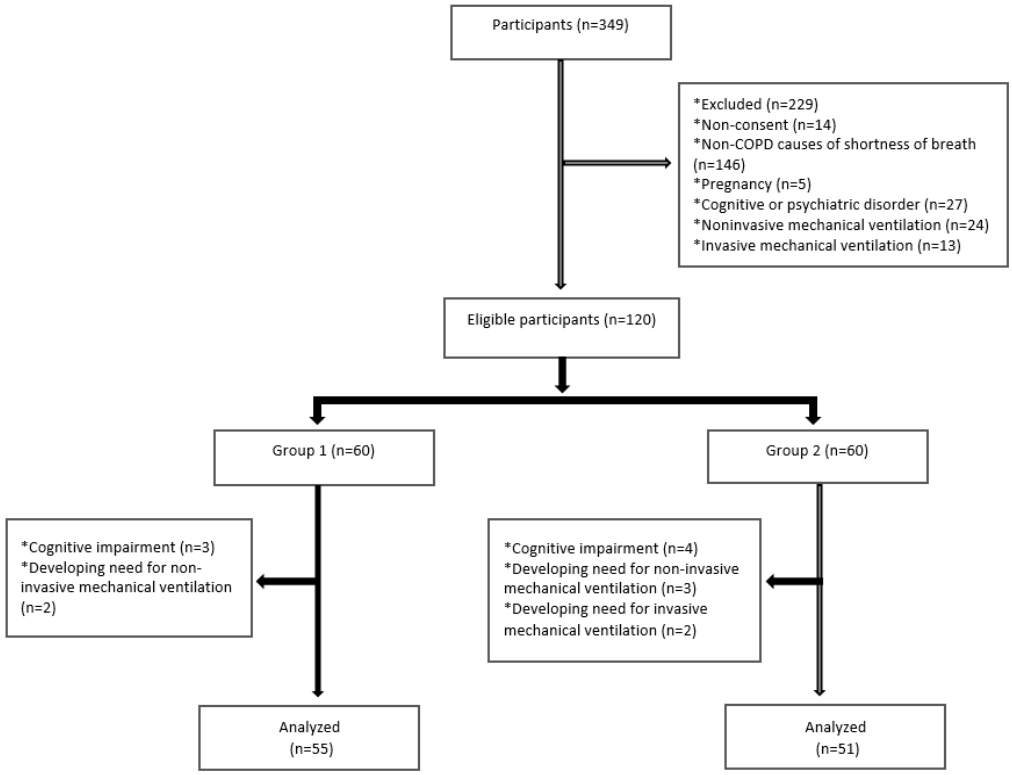

Figure 1 Flow chart of the study

3. Results

A total of 349 patients were included in the study. According to the inclusion and exclusion criteria, 120 patients were eligible for the study. The patients were assigned to the groups according to the randomization table. While the treatment of the patients was continuing, patients who developed impaired consciousness and need for mechanical ventilation were excluded from the study. Accordingly, 51.9% (n = 55) of the analyzed patients constitute the patients in group 1 (Figure 1).

Table 1 Demographics and clinical characteristics of all patients

Variables	Values
Age, years, mean±SD (min-max)	69.9±10 (44-90)
Gender, male, n (%)	66 (62.3%)
Smoking, n (%)	68 (64.2%)
Smoking, pack/year, mean±SD (min-max)	9±8 (0-30)
Smoke exposure, n (%)	20 (18.9%)
Capacitor presence, n (%)	74 (69.8%)
Chronic diseases, n (%)	
COPD	42 (39.6%)
COPD+CAD	37 (34.9%)
COPD+HT	9 (8.5%)
COPD+HT+DM	8 (7.5%)
Other	10 (9.5%)
Vital signs in arrival, Median (IQR)	
Systolic blood pressure (mmHg)	130 (19)
Diastolic blood pressure (mmHg)	80 (20)
Heart rate (BPM)	96 (28)
Fever (°C)	36.4 (12)
Respiratory rate (BrPM)	26 (11)
Oxygen saturation level (%)	81 (12)
Before exacerbation treatment, Median (IQR)	
pH	7.41 (0.58)
pCO_2 (mmHg)	40.8 (12.7)
pO_2 (mmHg)	49.6 (19.4)
sO_2 (%)	81.2 (18.3)
HCO_3 (mEq/L)	25.2 (8.4)
Lactate (mmol/L)	1.8 (0.9)
Base gap (mmol/L)	0.75 (7.4)
White blood cell count (10^3/L)	9.85 (7.62)
Serum Creatinine (mg/dL)	0.9 (0.4)
After exacerbation treatment, Median (IQR)	
pH	7.42 (0.04)
pCO_2	40.5 (11.6)
pO_2	58.1 (24.3)
sO_2	89.4 (13.2)
HCO_3	25.3 (5.9)
Lactate	1.8 (1.1)
Base gap	0.55 (6.6)

SD: standard deviation, COPD: chronic obstructive pulmonary disease, CAD: coronary artery disease, HT: hypertension, IQR: interquartile range, pCO_2: partial pressure of carbon dioxide, pO_2: partial pressure of oxygen, sO_2: oxygen saturation, HCO_3: bicarbonate

The mean age of the patients was 69.9 ± 10 years, 66% were male, 64.2% were smoking and 69.8% had a history of using condenser at home. The socio-demographic and clinical characteristics of the patients and laboratory test results are shown in Table-1.

The mean age of the groups was 71.8 ± 9.7 and 67.9 ± 9.9 years, respectively, and it was statistically significant ($p = 0.044$). However, it was not statistically significant between the groups in terms of gender, smoking, amount of cigarettes smoked, exposure to smoke, presence of condenser, application to the emergency service and chronic disease ($p > 0.05$). When the vital signs of the patients were compared, blood pressure and heart rate were statistically significant ($p < 0.05$). After the treatment, statistical significance was found only in diastolic blood pressure ($p = 0.024$). There was no statistical significance between the groups in comparing the blood gas parameters of the patients before treatment ($p > 0.05$).

After acute exacerbation treatment, although it was determined that pCO_2 value decreased in both groups, statistical significance was not observed ($p > 0.05$). It was also found that pO_2 and sO_2 values increased more in the jet nebulizer group compared to the other group and were statistically significant ($p < 0.05$). The demographic and clinical comparative analysis of both groups are given in Table-2.

The data obtained in the comparison of the vital signs of the patients within the group, before and after treatments, are given in Figure 2. Accordingly, it was found that there was a significant decrease in systolic blood pressure change in both groups, but there was a significant decrease in diastolic blood pressure in group 2.

Table 2 Comparison of demographic and clinical characteristics of patients with COPD according to the groups

Variables	Group 1. Jet nebulizer (n=55)	Group 2. Central system oxygen therapy (n=51)	p value
Age, years, mean±SD (min-max)	71.8±9.7 (52-89)	67.9±9.9 (44-90)	0.044[a]
Sex, n (%)			
Female	23 (41.8%)	17 (33.3%)	0.368[b]
Male	32 (58.2%)	34 (66.7%)	
Smoking, Positive, n (%)	31 (56.4%)	37 (72.5%)	0.083[b]
Smoking, pack/year, mean±SD (min-max)	9±8 (0-25)	11±9 (0-30)	0.086[a]
Smoke exposure, n (%)	13 (23.6%)	7 (13.7%)	0.193[b]
Capacitor presence, n (%)	38 (69.1%)	36 (70.6%)	0.867[b]
Way of Coming, n (%)			
Ambulance	24 (43.6%)	17 (33.3%)	0.276[b]
Own possibilities	31 (56.4%)	34 (66.7%)	
Chronic Diseases, n (%)			
COPD	22 (40.0%)	20 (39.2%)	
COPD+HT	3 (5.5%)	6 (11.8%)	
COPD+ CAD	24 (43.5%)	13 (25.5%)	0.190[b]
COPD+ DM	-	3 (5.9%)	
COPD+HT+DM	3 (5.5%)	5 (9.8%)	
COPD+HT+CAD	3 (5.5%)	3 (5.9%)	
COPD+ HT+DM+CAD	-	1 (2.0%)	
Before exacerbation treatment, Median (IQR)			
Systolic blood pressure (mmHg)	130 (124-137)	138 (126-154)	0.007[c]
Diastolic blood pressure (mmHg)	78 (68-80)	87 (75-93)	0.000[c]

Variables	Group 1. Jet nebulizer (n=55)	Group 2. Central system oxygen therapy (n=51)	p value
Heart rate (BPM)	96 (68-110)	120 (92-113)	0.012[c]
Fever (°C)	36.5 (36.4-36.6)	36.3 (36.2-36.5)	0.052[c]
Respiratory rate (BrPM)	27 (21-32)	23 (19-30)	0.155[c]
Oxygen saturation level (%)	82 (75-88)	80 (73-86)	0.373[c]
After exacerbation treatment, Median (IQR)			
Systolic blood pressure (mmHg)	130 (120-130)	130 (120-140)	0.361[c]
Diastolic blood pressure (mmHg)	75 (72-80)	80 (71-87)	0.024[c]
Heart rate (BPM)	94 (72-96)	95 (81-110)	0.108[c]
Body temperature (°C)	36.5 (36.2-36.6)	36.5 (36.3-36.7)	0.501[c]
Respiratory rate (BrPM)	23 (20-29)	24 (20-30)	0.391[c]
Oxygen saturation level (%)	88 (85-90)	85 (82-90)	0.095[c]
Before exacerbation treatment, Median (IQR)			
pH	7.40 (7.37-7.42)	7.42 (7.37-7.47)	0.148[c]
pCO_2 (mmHg)	42 (24.7-49.6)	40.6 (33.3-46.7)	0.450[c]
pO_2 (mmHg)	47.7 (38.1-57.9)	51.7 (39.3-61.2)	0.150[c]
sO_2 (%)	78.4 (63.6-86.8)	84.5 (70.1-89.8)	0.112[c]
HCO_3 (mEq/L)	27.5 (21.9-30.9)	24.9 (22.5-28)	0.604[c]
Lactate (mmol/L)	1.8 (1.3-2.2)	1.6 (1.2-2.2)	0.399[c]
Base gap (mmol/L)	2.9 (-2.2-6)	0.5 (-0.8-4.7)	0.987[c]
White blood cell count (10^3/L)	9.6 (7.3-18.8)	9.5 (8.4-14.5)	0.313[c]
Serum Creatinine (mg/dL)	0.9 (0.7-1.1)	0.8 (0.7-1.1)	0.837[c]
After exacerbation treatment, Median (IQR)			
pH	7.41 (7.40-7.44)	7.42 (7.39-7.46)	0.304[c]
pCO_2 (mmHg)	40.5 (34.3-49)	40.2 (34.4-45.5)	0.711[c]
pO_2 (mmHg)	69.6 (44.8-82)	54 (46.7-60.1)	0.003[c]
sO_2 (%)	91.7 (78.2-94.6)	86.8 (81.5-90.6)	0.006[c]
HCO_3 (mEq/L)	25.4 (20.6-26.9)	24.8 (21.5-27.2)	0.761[c]
Lactate (mmol/L)	1.8 (1.1-2.2)	1.4 (1.1-2.3)	0.131[c]
Base gap (mmol/L)	1 (-3-3.7)	0.5 (-1.6-3.5)	0.778[c]

SD: standard deviation, COPD: chronic obstructive pulmonary disease, CAD: coronary artery disease, HT: hypertension, DM: diabetes mellitus, IQR: interquartile range, pCO_2: partial pressure of carbon dioxide, pO_2: partial pressure of oxygen, sO_2: oxygen saturation, HCO_3: bicarbonate. a Student's t-test b Chi-square statistic test c Mann-Whitney U test

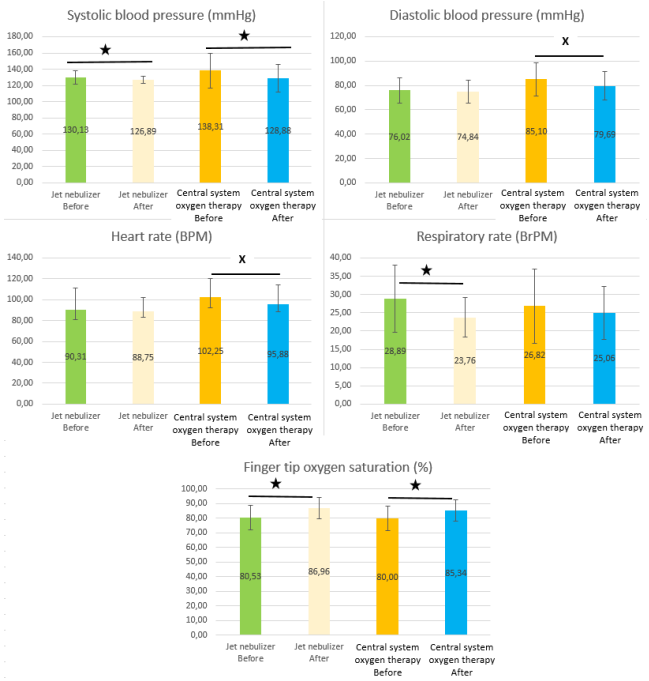

Figure 2 Comparisons of patients' vital signs before and after treatments ★: p<0.001 **x:** p<0.05

It was observed that the change in heart rate decreased in the treatment group with oxygen supply connected to the central system, while it was found that the respiratory rate decreased significantly in the jet nebulizer treatment group. It was found that fingertip oxygen saturation increased significantly after treatment in both treatment groups and was statistically significant (p <0.001).

The data obtained in the comparison of the arterial blood gas parameters of the patients within the group, before and after treatments, are given in Figure 3. Accordingly, it was found that pH, pO_2, sO_2 increased, pCO_2 decreased and were statistically significant in jet nebulizer treatment group (p <0.05). In the supply connected to the central system oxygen treatment group, it was found that only sO_2 increased, lactate decreased and these were statistically significant (p <0.05).

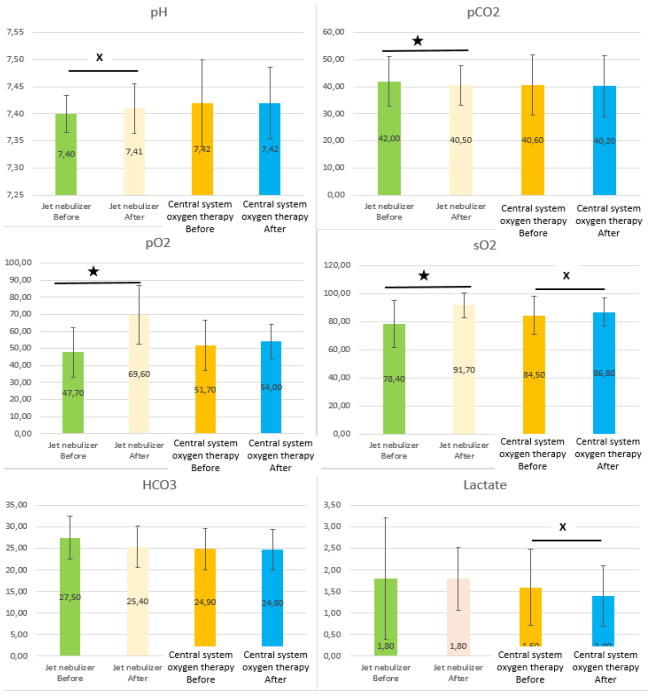

Figure 3 Comparisons of arterial blood gas parameters of patients before and after treatments. ★: p<0.001 **x:** p<0.05

4. Discussion

In this study, the same pharmacological treatment protocol was applied in different ways in the management of COPD acute exacerbation in the emergency department, and the efficacy of the treatments were investigated. Treatment efficacy in our study was decided according to the vital signs and changes in blood gas parameters of the patients at the time of admission and after acute exacerbation treatment. Accordingly, one of the vital signs, respiratory rate decreased more in jet nebulizer group and was statistically significant. Among the blood gas parameters, it was determined that pCO_2 decreased more in the jet nebulizer treatment group and was statistically significant. In addition, it was determined that pO_2 and sO_2 increased more in the jet nebulizer treatment group compared to the other group and were statistically significant.

Oxygen therapy is the primary treatment of acute exacerbation as stated in the COPD guidelines [2, 11, 12]. However, as a result of improper oxygen therapy in COPD, hypercapnia may deepen and respiratory depression may occur [6]. Although many complex and combined factors are held responsible for the hypercapnia that occurs, it has been emphasized that the oxygen given for treatment purposes in pre-hospital health services, during transports or sometimes in emergency departments, also plays an important role [12–14]. When high concentration of oxygen is given, the amount of oxygen in the blood increases, but the amount of CO_2 also increases [15]. In addition, another risk in COPD acute exacerbation patients treated with high concentrations of oxygen is that the hypoxia worsens with the cessation of oxygen therapy [15]. High concentrations of oxygen should not be given to prevent deep hypoxia, and oxygen therapy should be titrated and finished [12]. In this way, it should be aimed to keep the oxygen saturation of the patients within a certain range by applying controlled oxygen therapy. In our study, although the fingertip oxygen saturation of the patients at the time of admission to the emergency department was similar, the pO_2 and sO_2 in blood gas analysis were different and were lower in the jet nebulizer group. After treatment, pO_2 and sO_2 values increased significantly more in the jet nebulizer group and were found to be statistically significant. Acute exacerbation treatment was given to the patients in group 2 with oxygen from the hospital central oxygen system in our study. This shows us the importance of giving oxygen therapy in a controlled and titrated manner.

In the management of acute exacerbation of COPD in emergency departments, hypercapnia may occur due to the use of the hospital central oxygen system instead of using a nebulizer. This worsens both the clinic and the prognosis of the patients. In our study, hypercapnia was observed with a higher rate in group 2 patients treated with central oxygen system. Therefore, it was determined that more effective treatment was performed in group 1, who was treated with jet nebulizer.

Today, management of COPD acute exacerbation relies heavily on the use of a nebulizer. In addition, non-invasive and invasive mechanical ventilation may be required in severe acute exacerbations [6, 16, 17]. In many studies and meta-analyzes in the literature, the advantages and disadvantages of inhalation devices over each other have been emphasized [9, 16–20]. However, the real point in the management of COPD acute exacerbation is to aim to improve lung function, morbidity and mortality in the long term, together with effective treatment of acute exacerbation. For this, it is necessary to apply the right medicine, at the right dose, with the right device.

4.1. Limitations

Our study has some limitations. The study could not be done in double-blind method, because a nebulizer device was used in our study. Another limitation is that spirometric measurements were not performed in patients, at the time of admission and after treatment, due to the incompatibility and agitation of the patients due to air starvation during their emergency admissions. Finally, age, systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (BPM) values were statistically significantly lower in the nebulizer group.

5. Conclusion

COPD acute exacerbation patients need to be adequately oxygenated and stabilized in emergency departments without delay. In addition, oxygen and inhaler treatments constitute the cornerstone of acute exacerbation management of COPD in emergency departments. It is very important to apply inhaled treatments with appropriate devices. In the present study, it was found that the blood gas parameters of patients treated with nebulizers recovered better than the group treated with a reservoir mask. Therefore, it is recommended to apply the treatment of acute exacerbation of COPD with nebulizers in the emergency department.

Conflict of Interest and Funding

None of the authors have commercial interests, financial interests and/or other relationships with the manufacturers of pharmaceuticals, laboratory supplies and/or medical devices, or with commercial providers of medically related services.

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